studies and need replication in clinical trials, suggest that NSAIDs may be effective chemopreventive agents in reducing risk of neoplastic progression in persons with Barrett's esophagus.

#B114 Insulin-like Growth Factors and Risk of Neoplastic Progression to Esophageal Adenocarcinoma in Persons with Barrett's Esophagus. Sid H. Siahpush,[1] Thomas L. Vaughan,[1] Carissa Sanchez,[1] S Kay Lewis,[1] Robert D. Odze,[2] Peter S. Rabinovitch,[3] Brian J. Reid.[1] Fred Hutchinson Cancer Research Center,[1] Seattle, Brigham & Women's Hospital,[2] Boston, University of Washington,[3] Seattle.

Insulin-like growth factor-I (IGF-I) and its main binding protein (IGFBP-3) have been reported to be related to the risk of several cancers. However, they have not been studied extensively in relation to esophageal adenocarcinoma (EA). We used data and specimens collected in an ongoing cohort study of predictors of neoplastic progression in persons with the precancerous condition Barrett's esophagus (BE) (n = 347, up to 8 years of follow up) to determine whether serum concentrations of IGF-I and IGFBP-3 were related to risk of EA and two precursor lesions, aneuploidy and tetraploidy. The subjects donated blood and underwent endoscopic biopsies, physical examination and interview at baseline and periodic follow-up visits. IGFs concentrations were measured using two-site immuno-radiometric assay (IRMA) kits. Cox regression models were used to calculate adjusted hazard ratios (HRs). Serum levels of IGF-I (comparing above and below the median) were not associated with EA (HR = 1.3, 95% CI: 0.7- 2.5), aneuploidy or tetraploidy. Similar results were observed for the ratio IGF-I/IGBP-3. Higher concentrations of IGFBP-3 were associated with an increased risk of aneuploidy (HR= 2.3, 95% CI: 1.1- 4.8) but not other outcomes. The above results did not change substantially after adjustment for sex, age, BMI, waist-to-hip ratio, smoking status, selenium blood levels or NSAID use. More detailed analyses using IGF-I values divided into quartiles or as continuous variables did not alter the conclusions. Serum selenium levels at baseline modified the association between IGFBP-3 levels and risk of EA (p=0.02), such that the positive (but insignificant) association with IBFBP-3 was strengthened and became significant among persons with higher selenium levels. The number of events observed in the cohort thus far would enable the detection of relative risks between 2.5 and 3.0; thus the lack of association between IGF-1 levels and risk of neoplastic progression may be due in part to relatively modest statistical power. However, we did observe that higher concentrations of IGFBP-3 were related to risk of aneuploidy. This is consistent with studies of IGFBP-3 and premenopausal breast cancer. The observed interaction between selenium blood levels, IGFBP-3 and EA are consistent with experiments in human and animal prostate cancer cell lines that suggest a role for selenium in the regulation of IGFBP-3. Further exploration of the joint effects of IGF-I, IGFBP-3 and selenium in the development of EA is needed to clarify these relationships.

#B115 Correlates of microsatellite instability in a population based study of colorectal cancer in Israel. Gad Rennert,[1] Ronit Almog,[1] Joel K. Greenson,[2] Marcelo Low,[1] Lynn Tomsho,[3] Hedy S. Rennert,[1] Joseph D. Bonner,[3] Stephen B. Gruber.[3] CHS National Cancer Control Center and Department of Community Medicine and Epidemiology, Carmel Medical Center and Technion,[1] Haifa, Israel, Department of Pathology, University of Michigan,[2] Ann Arbor, MI, Division of Molecular Medicine and Genetics, University of Michigan,[3] Ann Arbor, MI.

The Molecular Epidemiology of Colorectal Cancer (MECC) study is a population based study of cases of colorectal cancer diagnosed in a defined population in Northern Israel over a five year period. Among the study aims is the estimation of the fraction of cases possibly attributed to HNPCC (Hereditary Non-Polyposis Colon Cancer). Thus far, tissue samples of 1,262 cases have been tested for microsatellite instability using five markers recommended by an NIH consensus panel (BAT25, BAT26, D5S346, D2S123, D17S250). Of these, instability of at least one marker was found in 289 cases (22.9%). In 123 cases (9.8%) at least two markers exhibited instability, corresponding to the MSI-High (microsatellite instable) consensus definition. Eleven percent (11.9%) of tumors in females and 7.7% in males had MSI-H tumors. Among MSI-H cases whose primary tumor site was known, 85/108 (78.7%) had right-sided colon cancer which is in line with previously reported characteristics of the disease. The mean age in these subjects was 70 with no difference between MS-Instable and MS-Stable cases (p-value = 0.44). Median survival time was significantly improved in the MSI-H group (32.6 months) compared to those with MS-Stable tumors (29.9 months, Hazard Ratio 0.64, 95% CI 0.46-0.92, p =0.015). However, when controlling for age at diagnoses and stage at presentation the difference in survival between MS-Instable and MS-Stable cases was less prominent (p-value=0.078). Preliminary analyses of the putative protective association of aspirin with colorectal cancer demonstrated that aspirin use was associated with a 23% reduction in risk of MS-Stable colon cancer (OR=0.77 95% Confidence Interval 0.67-0.87), but no appreciable association was observed in the MSI-High cases (OR = 1.06, 95% CI 0.63-1.79, p = 0.21 for heterogeneity). MSI-High tumors represent a clinically distinct group of colorectal cancers that warrant further epidemiologic study.

#B116 Glutathione S-transferase M1, P1, and T1 polymorphisms and prostate cancer risk in middle-aged men. Ilir Agalliu, Wendy J. Langeberg, Claudia A. Salinas, Lori Iwasaki, Ziding Feng, Janet L. Stanford. Fred Hutchinson Cancer Research Center, Seattle, WA.

Background: The glutathione S-transferases (GST) are phase-II detoxification enzymes involved in the metabolism of carcinogenic substances and reactive oxygen compounds. Genetic polymorphisms in allelic variants of GST-M1, P1, and T1 have been linked to prostate cancer, however the evidence is inconsistent. The aim of this study was to further evaluate the relationships between genetic polymorphisms in these GSTs and prostate cancer and to assess whether associations vary according to environmental exposures. **Methods:** Cases (n=753) were men residing in King County, WA, aged 40-64 years, who were diagnosed with prostate cancer from 1993 through 1996 and identified via the Seattle-Puget Sound SEER cancer registry. Controls (n=703) were male residents of King County, identified via random digit dialing, and frequency age-matched to cases. Subjects completed a survey and genomic DNA was purified from peripheral lymphocytes. Specific genotypes were identified via PCR analysis. Data analysis was restricted to Caucasians (95.5% of the study population). Logistic regression was used to assess the relationship between genotypes and prostate cancer. Multiplicative models were used to assess gene-gene and gene-environment interactions. **Results:** The percentage of men with the GSTM1-null genotype was higher among cases compared to controls (55.6% vs. 47.5%). There was no difference, however, between groups according to GSTT1 or P1 (I105V) genotypes. There was an increased risk of prostate cancer for the GSTM1-null genotype (OR 1.54; 95%CI 1.19-2.01); and no associations for either GSTT1 or P1 genotypes. When looking at combined M1 and T1 genotypes, the highest risk was among men with GSTM1-null and GSTT1-present (OR 1.44; 95%CI 1.11-1.88). We evaluated the GSTM1 association with other exposures, such as smoking and cruciferous vegetable consumption, which also affect the oxidative stress pathway. Data supported an interaction between the GSTM1 genotype and intensity of smoking (cigarettes/day), with an increased risk for subjects who were GSTM1-null and smoked 21-30 and ≥ 31 cigarettes/day; ORs of 2.39 (95% CI 1.04-6.56) and 3.63 (95%CI 0.77 – 5.34), respectively, compared to GSTM1-present, nonsmokers. Among men with the GSTM1-null genotype, there was a trend (p = 0.04) of increasing risk with increasing numbers of cigarettes smoked per day. There was no interaction between GSTM1 genotype and cruciferous vegetable intake. **Conclusions:** Risk of prostate cancer was not associated with either GSTT1 or P1 (Ile105Val) polymorphisms. However, men with the GSTM1-null genotype had a moderately increased risk of prostate cancer. There was also an interaction between GSTM1 genotype and intensity of smoking, with the highest ORs observed for GSTM1-null smokers of >1 pack/day. These findings suggest that GSTM1 genotype defines a subgroup of men at higher risk of prostate cancer, particularly if they are heavy smokers. This observation is consistent with the role of GST enzymes in detoxifying environmental carcinogens such as benzo[a]pyrene, found in cigarette smoke.

#B117 Common Variants in Selected Metabolic Genes and the Risk of Adult Brain Tumors. Anneclaire J. De Roos,[1] Nathanial Rothman,[2] Merideth Brown,[3] Peter D. Inskip.[2] University of Washington Department of Epidemiology and the Fred Hutchinson Cancer Research Center,[1] Seattle, WA, Division of Cancer Epidemiology and Genetics, National Cancer Institute,[2] Bethesda, MD, Core Genotyping Facility, National Cancer Institute,[3] Frederick, MD.

Genes involved in Phase I and Phase II metabolism of aromatic hydrocarbons exhibit sequence variability that may mediate the risk of adult brain tumors. We evaluated associations between gene variants in *CYP1A1*, *CYP1B1*, *GSTM3*, *EPHX1*, and *NQO1* and adult brain tumor incidence. Cases were 782 patients with intracranial glioma, menin-

glioma or vestibular schwannoma diagnosed from 1994 to 1998 at three U.S. hospitals. Controls were 799 patients admitted to the same hospitals for non-malignant conditions. DNA was extracted from blood samples that had been collected on 1,277 subjects, and genotyping was successfully conducted for *CYP1A1 I462V, CYP1B1 V432L, EPHX1 Y113H, GSTM3* intron 6 deletion, and *NQO1 P187S*. The *CYP1B1 V432L* homozygous variant was associated with decreased risk of meningioma (odds ratio [OR]=0.6, 95% confidence interval [CI]: 0.3-1.0), but not the other tumor types. The *GSTM3* *B/*B variant genotype was associated with increased risk of glioma (OR=2.3, 95% CI: 1.0-5.2) and meningioma (OR=3.6, 95% CI: 1.3-9.8). Increased risks associated with the *GSTM3* *B/*B were observed in younger (<50 years) and older patients (≥50 years), in men and women, and within each study site. The magnitude of association for *GSTM3* with glioma and meningioma was greater among ever-smokers compared to those who had never smoked (for glioma: smokers, OR=4.1, 95% CI: 1.3-12.6; never-smokers, OR=2.0, 95% CI: 0.4-9.7). None of the other genotypes showed consistent associations with any tumor type. The association with the *GSTM3* variant, while intriguing, should be viewed with skepticism until replicated in another study population, since a previous study found no such association with glioma, and the tissue-specific activity of the two alleles is unclear. Our findings will inform future research on metabolic genes and their substrates as potential causes of brain tumors.

#B118 MTHFR variants reduce the risk of C>T transitions within the *p53* tumor suppressor gene in colon tumors, but are not associated with microsatellite instability. Cornelia M. Ulrich,[1] Karen Curtin,[2] Wade Samowitz,[2] Jeannette Bigler,[1] Bette Caan,[3] John D. Potter,[1] Martha L. Slattery.[2] Fred Hutchinson Cancer Res. Center,[1] Seattle, WA, University of Utah,[2] Salt Lake City, Kaiser Permanente Medical Care,[3] Oakland, CA.

Background: 5,10-methylene-tetrahydrofolate reductase (MTHFR) is a key enzyme in folate metabolism. Changes in enzyme function affect the distribution of folate metabolites towards either the provision of methyl groups or nucleotide synthesis. Lower MTHFR activity has been previously associated with microsatellite instability and genomic DNA hypomethylation. Methylated cytosines at *CpG* sites are more likely to be mutated and have been implicated in *C>T* transitions in the *p53* tumor suppressor gene. We investigated two polymorphisms in the *MTHFR* gene (*C677T* and *A1298C*) and their associations with colon tumor characteristics, including mutations in *k-ras* or *p53* and microsatellite instability (MSI). **Methods:** The study population comprised 1248 colon cancer cases and 1972 controls who participated in a large population-based multi-center case-control study. They had been previously analyzed for tumor mutations in *k-ras*, *p53*, as well as MSI and *MTHFR* genotypes. We performed both case-control and case-case analyses with respect to the tumor characteristics. Multivariable-adjusted odds ratios for the case-control comparison are presented. **Results:** Overall, *MTHFR* genotypes were not associated with MSI status or the presence of any *p53* mutation. Individuals with variant *MTHFR* genotypes or the *677C-1298C* haplotype had a modestly reduced risk of *k-ras* positive tumors (*677TT* vs *677CC(ref)* OR=0.7, 95% CI 0.4-1.0; *1298AC* vs *1298AA(ref)* OR=0.8 (0.6-1.0); *1298CC* vs *1298AA(ref)* OR=0.8 (0.5-1.2)). Individuals with homozygous variant *MTHFR* genotypes had a significantly reduced risk of *C>T* transitions within the *p53* gene (*677TT* vs *677CC(ref)* OR=0.3 (0.1-0.8); *1298CC* vs *1298AA(ref)* OR=0.5 (0.2-1.0)). The *MTHFR 677T-1298A* haplotype was associated with a borderline significantly reduced risk of *C>T* transitions (OR=0.8 (0.6-1.0)). *MTHFR* genotypes were not associated with other types of mutations in the *p53* gene. Mutational hotspots within *k-ras* did not include *C>T* transitions. **Conclusions:** Our study does not confirm a previous report linking MTHFR genotypes to microsatellite instability. However, reduced MTHFR activity was associated with a statistically significant decreased risk of *C>T* transitions within the *p53* gene. We hypothesize that this relationship may be attributable to some degree of reduced genomic DNA methylation, resulting in a lower probability of spontaneous deamination of methylated cytosine to thymidine. These results require confirmation, yet suggest that investigations of tumor spectra on a population level may yield insight in possible mechanisms linking folate metabolism to carcinogenesis.

#B119 Lack of association between promoter polymorphism in the matrix metalloproteinase-1 and risk of cervical cancer in Korean women. Woong Ju. Seoul National University Hospital, Seoul, Korea.

Purpose: The aim of this investigation was to analyze the association between a single nucleotide polymorphism (SNP) in the MMP-1 promoter gene -1607 bp region and cervical cancer risk in Korean women. **Materials and Methods:** The blood samples of 232 cervical cancer patients and 332 non-cancer control subjects who managed at Seoul National University Hospital from 1999 to 2002 were collected. Polymorphism in MMP-1 promoter -1607 region was determined using TaqMan method. Allele frequency and genotype distribution in the cervical cancer group were compared with those of the control group to determine whether this polymorphism elevates the susceptibility of Korean women to cervical cancer. The relationship between this SNP and cancer invasiveness was also evaluated by collating clinicopathologic data of those in the cancer group, such as FIGO stage, histologic type, and the status of lymph node and parametrial invasion. **Results:** In the cervical cancer group, the allele frequency of 2G was 66.1%, in the control group 68.2%, showing no significant difference (p=0.41). Similarly the genotypes with insertion (2G/2G) or deletion (1G/1G) polymorphism showed no increased risk for cervical cancer susceptibility compared with 1G/2G genotype. A subgroup analysis of the clinicopathologic parameters in cancer group also showed no significant difference suggesting the lack of an association between SNP of the MMP-1 promoter -1607 bp region and cervical cancer invasiveness. **Conclusion:** This study shows that Korean with specific polymorphism in MMP-1 are neither more susceptible to develop cervical cancer nor more vulnerable for cancer progression.

#B120 Vitamin D Receptor (VDR) Gene Polymorphisms (Bsm1, Fok1, Cdx2) in Total Prostate Cancer (CaP) Risk among United States Men. Bahar Mikhak, David Hunter, Donna Spiegelman, Edward Giovannucci. Harvard School of Public Health, Boston, MA.

Vitamin D maintains calcium homeostasis and regulates growth and differentiation of many types of cells. The antiproliferative effects of vitamin D require the expression of the nuclear vitamin D receptor (VDR). Circulating 1,25(OH)2D binds to VDR in prostatic epithelial cells and sets in motion a series of events that leads to the regulation of cancer-related genes. Most data indicate that the Fok1 F allele is more effective than the f allele in transactivation of the 1,25(OH)2D signal. The Bsm1 polymorphism was found to be functional in a study since controls with BB genotype were shown to have a significantly higher levels of 1,25(OH)2D than those with the Bb or bb genotypes. An A/G substitution is reported in the cis element of the promoter to interact with caudal related homeodomain transcription factor CDX-2. We investigated the role of VDR gene polymorphisms Fok1, Bsm1, and Cdx2, in relation to risk of developing CaP using the blood data collected from 18,018 members of the Health Professional Follow-up Study in 1993-1995. We conducted a nested case-control study consisting of 693 incident cases up to January 2000 and 693 matched controls. Controls who had a PSA test following the blood draw and were free of CaP were selected using a risk-set incidence density sampling method. Matching factors were: age, history of a PSA test before blood draw, time of day, season and year of blood draw. Genotypes were determined using Taqman. The VDR genotypes were assessed in individual models as main effects for the development of CaP. No dose-response trend in CaP risk was observed with the increase in the number of variant alleles, so genotypes were entered into the model as indicator variables. We found the direction of the non-significant associations for the Fok1 and Cdx2 alleles to be consistent with those previously stated in the literature. Men with two copies of the Fok1 variant allele f/f had a non-significant lower risk compared to those with F/F and F/f genotypes (OR= 0.90, 95% CI: 0.65-1.25) and men with two copies of the Cdx2 variant allele A/A had a non-significant lower risk compared to those with G/G and A/G genotypes (OR= 0.91, 95% CI: 0.72-1.14). In contrast to previous studies' findings, men with two copies of the Bsm1 variant allele B/B had a non-significant higher risk compared to those with b/b and B/b genotypes (OR= 1.23, 95% CI: 0.92-1.66). Furthermore, Fok1, Bsm1 and Cdx2 polymorphisms did not modify the relationship between family history and region of residence and CaP risk. In conclusion, we found no statistically significant main genotype effects or interactions with family history or region for Fok1, Bsm1 and Cdx2 on total CaP risk. However, our cases were comprised primarily of early-stage, PSA-detected CaP and effect of VDR polymorphisms on cancer progression can not be ruled out. Next, we plan to study whether the VDR polymorphisms modify the relationship between plasma vitamin D levels and total and advanced CaP risk among this cohort of men.